CLAIMS

What is claimed is:

1. A method comprising:

   a) using an exonuclease to release unlabeled nucleotides from one end of one or more nucleic acid molecules;

   b) separating the nucleotides from the exonuclease and the one or more nucleic acid molecules;

   c) identifying the unlabeled nucleotides by Raman spectroscopy; and

   d) determining the sequence of the nucleic acid from the identified nucleotides.

2. The method of claim 1, wherein single molecules of unlabeled nucleotides are identified by Raman spectroscopy.

3. The method of claim 2, wherein a single nucleic acid molecule is sequenced.

4. The method of claim 1, wherein multiple nucleic acid molecules are sequenced simultaneously.

5. The method of claim 1, wherein the one or more nucleic acid molecules is attached to a surface.

6. The method of claim 1, wherein the nucleotides are identified by surface enhanced Raman spectroscopy (SERS), surface enhanced resonance Raman spectroscopy (SERRS) and/or coherent anti-Stokes Raman spectroscopy (CARS).

7. A method comprising:

   a) sequentially removing nucleotides from one end of one or more nucleic acid molecules;

   b) attaching each nucleotide to at least one nanoparticle;

   d) identifying the nucleotides by Raman spectroscopy; and

   e) determining the sequence of the nucleic acid.

8. The method of claim 7, wherein single molecules of nucleotides are identified by Raman spectroscopy.

9. The method of claim 8, wherein a single nucleic acid molecule is sequenced.

10. The method of claim 7, wherein the nucleotides are unlabeled.

11. The method of claim 7, wherein the nanoparticles are modified with one or more linker compounds.

12. The method of claim 11, wherein the nucleotides are covalently attached to the linker compounds.

13. The method of claim 12, wherein the linker compound is 3-glycidoxypropyltrimethoxysilane (GOP).

14. The method of claim 7, wherein the nucleotides are attached to nanoparticles after the nucleotides are removed from the nucleic acid.

15. The method of claim 7, wherein the nucleotides are attached to nanoparticles before the nucleotides are removed from the nucleic acid.

16. The method of claim 15, wherein nanoparticles are attached to the 3' end of the nucleic acid.

17. The method of claim 7, wherein said nucleotides are identified by surface enhanced Raman spectroscopy (SERS), surface enhanced resonance Raman spectroscopy (SERRS) and/or coherent anti-Stokes Raman spectroscopy (CARS).

18. The method of claim 7, further comprising separating the nucleotides from the one or more nucleic acid molecules.

19. The method of claim 7, wherein an exonuclease is used to remove the nucleotides from said nucleic acid.

20. The method of claim 16, wherein the nucleotides are removed by acid hydrolysis.

21. The method of claim 20, further comprising using acid hydrolysis to remove the purine or pyrimidine base from the nucleotide.

22. A method comprising:

a) obtaining nucleotides that are attached to Raman labels;

b) synthesizing a nucleic acid comprising labeled nucleotides;

c) removing nucleotides from one end of the nucleic acid;

d) identifying the nucleotides by Raman spectroscopy; and

e) determining the sequence of the nucleic acid.

23. The method of claim 22, wherein single nucleotide molecules are identified by Raman spectroscopy

24. The method of claim 22, wherein each type of nucleotide is labeled with a distinguishable Raman label.

25. The method of claim 22, wherein only pyrimidine nucleotides are labeled with Raman labels.

26. The method of claim 22, further comprising: (i) obtaining at least one template nucleic acid molecule; (ii) hybridizing the template nucleic acid molecule to a primer; and (iii) adding a DNA polymerase to synthesize said nucleic acid.

27. An apparatus comprising:

a) a reaction chamber;

b) a microfluidic channel in fluid communication with the reaction chamber;

c) a flow-through cell in fluid communication with the microfluidic channel; and

d) a Raman detection unit operably coupled to the flow-through cell.

28. The apparatus of claim 27, wherein the Raman detector is capable of detecting single molecules of nucleotides.

29. The apparatus of claim 28, wherein the nucleotides are unlabeled.

30. The apparatus of claim 27, further comprising nanoparticles in the flow-through cell.